Darier disease, radiation therapy, and herpesvirus—an unfortunate triad

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Abstract

Darier disease (DD) is a rare autosomal dominant keratinizing disorder often characterized by brown scaly pruritic papules over the face, neck, and trunk. Herein is reported a patient who developed secondary cutaneous herpes simplex virus (HSV) following exacerbation of his DD as a result of radiation therapy. In November 2020, a 78-year-old man presented to clinic for a pruritic rash on his back consistent with DD. He had developed the rash after the conclusion of chemoradiation therapy for recently diagnosed urothelial carcinoma of the bladder with squamous differentiation. However, he returned two weeks later complaining of a marked worsening of the rash associated with a pain and burning sensations. Histopathology was non-conclusive, but the lesions were found to be positive for HSV-1 by PCR. The patient recovered without complication over a period of two weeks following a course of valacyclovir. There is precedent in the literature for ionizing radiation inducing flares of DD lesions in overlying skin. In addition, DD has been shown to put a patient at increased risk for secondary infections such as HSV. This case report demonstrates that HSV could pose a significant risk to those with DD receiving radiation therapy and thus could warrant prophylactic treatment.

Keywords: Darier disease, eczema herpeticum, herpes simplex, Kaposi varicelliform eruption, radiation oncology, radiation therapy

Introduction

Darier disease (DD) is a rare autosomal dominant keratinizing disorder that results from a mutation in the *ATP2A2* gene. Patients with this condition develop brown scaly pruritic papules over the face, neck, and trunk, although the extent of involvement is variable. Active DD can put a patient at increased risk for secondary infection. The occurrence of cutaneous herpes simplex virus (HSV) with DD is an established example, albeit rare. Secondary cutaneous HSV can be associated with a number of different clinical disorders characterized by cutaneous barrier dysfunction, the prototype being atopic dermatitis. When it occurs in this setting it is referred to as eczema herpeticum (EH). When it arises in other clinical settings such as DD, mycosis fungoides, pemphigus vulgaris, ichthyosiform erythroderma, Hailey–Hailey disease, psoriasis, and severe thermal burns, it is typically referred to as Kaposi varicelliform eruption (KVE) [1]. Kaposi varicelliform eruption and EH should be considered dermatologic emergencies and prompt diagnosis and treatment with antiviral therapy is necessary to prevent complications. In high-risk situations, prophylactic measures may even be considered. We report a patient who developed KVE following exacerbation of his DD resulting from radiation therapy for bladder cancer.

Case Synopsis

A 78-year-old man presented to our dermatology clinic for a painful rash on his back. His medical history was significant for recently-diagnosed urothelial carcinoma of the bladder with squamous differentiation, for which he was receiving chemoradiation (5-fluorouracil + mitomycin; pelvic radiation delivered with photon-based intensity

modulated radiation therapy to a total dose of 55Gy in 20 fractions). He also had a history of DD.

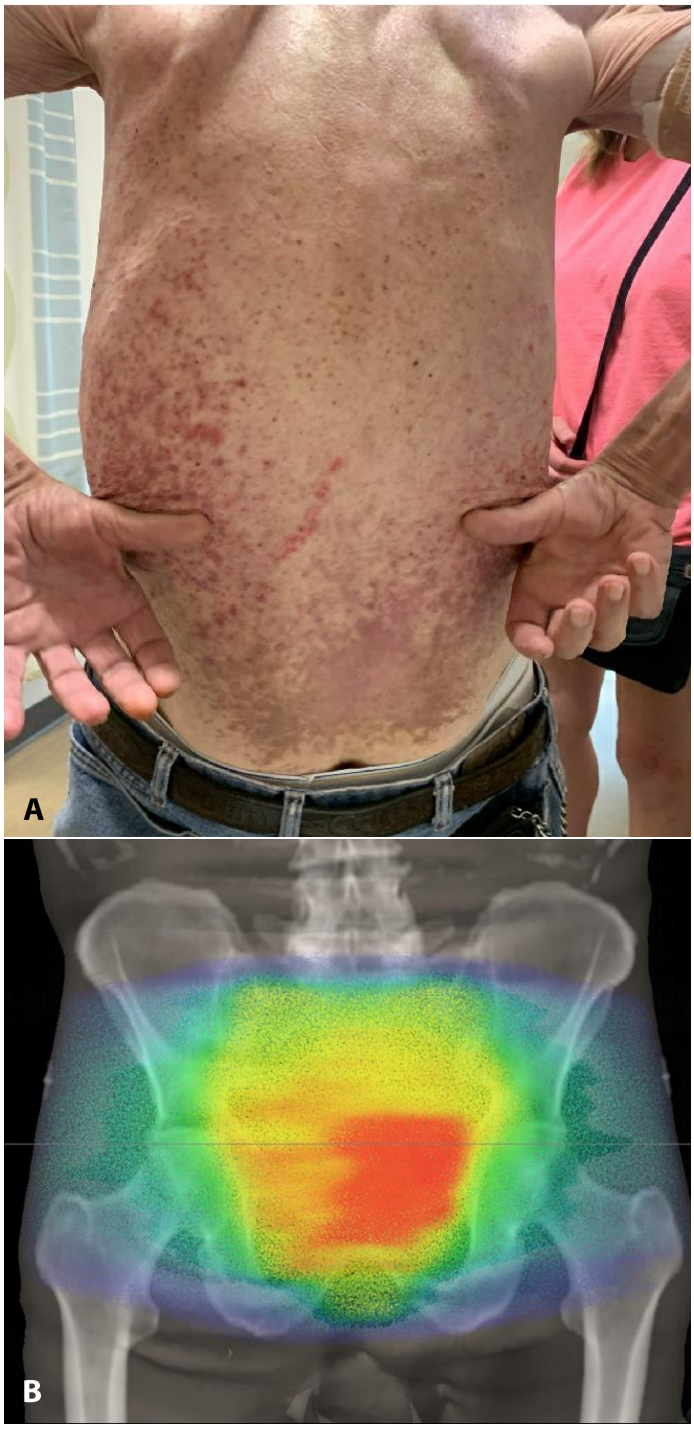

Figure 1. ***A)*** *Brown scaly papules consistent with Darier disease on the sacral region of the lower back.* ***B)*** *PA view of dose distribution associated with intensity-modulated photon radiation therapy. Color changes indicate radiation dose, with blue being a lower dose and red being a higher dose. Both photos were taken by radiation oncologist one week after the conclusion of radiation therapy, by which time the rash had migrated superiorly from the pelvis.*

During his final week of radiation therapy, he developed a circumferential pelvic rash in his radiation fields believed by his radiation oncologist to be consistent with a flare of DD (**Figure 1**). The patient was treated with oral acetretin and triamcinolone 0.1% cream. Three weeks after the onset of his rash, additional brown scaly papules consistent with DD appeared outside the radiation fields on his pre-sternal chest and back.

Our initial dermatologic examination, which occurred after his radiation therapy had concluded, revealed a well-appearing senior man with skin changes on his chest and lower back typical of DD. He felt the skin changes were improving with his ongoing acetretin and triamcinolone cream treatment.

He returned two weeks later complaining of a marked worsening of the rash, now with associated pain and burning sensations. Examination at that time revealed grouped flat-topped papules, vesicles, and pustules with underlying erythema on the mid back, lower back, and flanks, bilaterally (**Figure 2**). In addition, there were scattered DD-like lesions on his chest and back. Review of systems was otherwise negative.

A lesional punch biopsy was performed for histopathology (**Figure 3**) and a swab for herpes

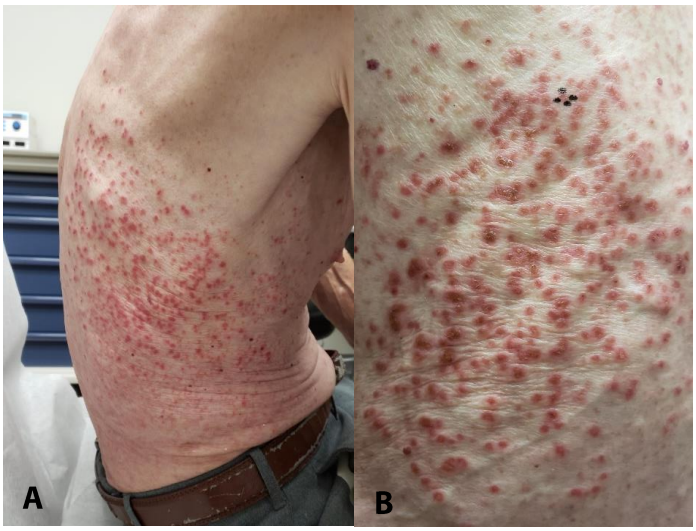

Figure 2. ***A)*** *Flat topped papules, vesicles, pustules, and underlying erythema on the right trunk.* ***B)*** *Punctate erythematous lesions on the left trunk. The four black ink dots in the upper part of this image indicate the site of the lesional biopsy.*

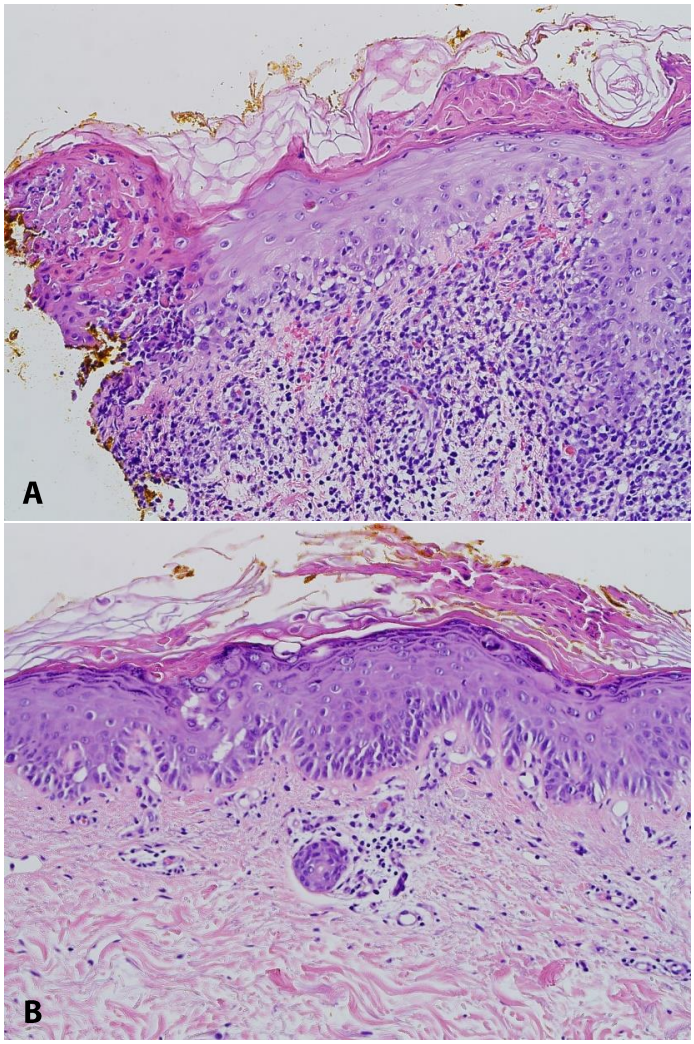

Figure 3. *H&E histopathology demonstrates **A)** lichenoid/interface dermatitis with superficial epidermal necrosis highly suspicious for herpesvirus infection, 100×, and **B)** focal acantholytic dyskeratosis with overlying scale crust consistent with Darier disease, 200×.*

virus PCR was obtained from the left flank to assess for herpes simplex and herpes zoster. The patient was started empirically on oral valacyclovir 1000mg by mouth three times daily for 7 days.

Histopathologic evaluation demonstrated superficial epidermal necrosis with lichenoid/interface dermatitis and many Civatte bodies in addition to focal acantholytic dyskeratosis with overlying scale crust. Cytopathologic changes were highly suspicious for, but not definitively diagnostic of herpesvirus infection. There were also collections of bacterial cocci in the overlying crust consistent with secondary impetiginization. Ultimately, the skin lesions were found to be positive for HSV-1 by PCR and the patient fully recovered without complication over a period of two weeks following the course of valacyclovir.

Case Discussion

We report a case of HSV-1 KVE that developed following exacerbation of a senior man's DD by radiation therapy for bladder cancer. Interestingly, both clinical examination and histopathology were complicated by multiple findings (DD, herpesvirus infection, and secondary impetigo) that made definitive diagnosis challenging. It was only after PCR demonstrated active HSV-1 infection that a consensus diagnosis could be reached.

Exacerbations of DD have been associated with exposure to heat, sunlight, UVB, lithium, oral corticosteroids, and mechanical trauma [2]. There is also precedent in the literature for ionizing radiation therapy inducing flares of DD lesions in overlying skin. In one case report, an adult woman without prior history of DD developed genetically-confirmed DD skin lesions in the pelvic area following therapeutic radiation therapy for cervical cancer. Similar to our case, that patient's DD lesions extended beyond the pelvic radiation fields to include the scapular, scalp, and lower abdominal regions [3]. Conversely, there is also support in the literature for radiation therapy resulting in the disappearance of pre-existing DD skin lesions of a patient receiving radiation therapy for non-small cell lung cancer in the radiation fields after an initial exacerbation [4].

In addition to inducing DD skin lesions, ionizing radiation therapy has been reported to be capable of inducing clinical reactivation of HSV [5,6]. It is conceivable that the radiation therapy induced DD and HSV skin changes concurrently in our patient. However, the clinical descriptions by the two clinicians who initially examined the skin changes that developed in the radiation fields in our patient were not suggestive of typical HSV or herpes zoster lesions. In addition, skin lesions in our patient were positive for HSV1. Herpes reactivation in the lumbar or sacral paraspinal ganglia is typically HSV2 rather than HSV1. The patient had no reported history of

cold sores, genital herpes, or shingles and did not recall any sick contacts.

Conclusion

Darier disease can place patients at risk for secondary viral and/or bacterial skin infections. In the absence of prompt antiviral therapy, EH and KVE can rapidly spread, resulting in severe morbidity and mortality [7]. For those at high risk, prophylactic treatment with oral acyclovir or valacyclovir is often recommended along with close surveillance and aggressive treatment for secondary bacterial infection.

However, in cases of DD, the increased risk of KVE secondary to radiation-induced exacerbation has not been explored or appropriately factored into the routine care of DD [8]. For this patient, HSV1 infection was not immediately apparent and the patient's infection was initially presumed to be a second exacerbation of DD, delaying appropriate treatment. This case report suggests that KVE could pose a significant risk to those with DD receiving radiation therapy and thus could warrant prophylactic treatment.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Tayabali K, Pothiwalla H, Lowitt M. Eczema herpeticum in Darier's disease: a topical storm. *J Community Hosp Intern Med Perspect.* 2019;9:347–50. [PMID: 31528287].
2. Mahboob A, Yaqub F, Shahzad Z, et al. Classical presentation of Darier's disease: a rare disorder of keratinisation. *J Ayub Med Coll Abbottabad.* 2010;22:230–3. [PMID: 22338464].
3. Chopra S, Sharma V, Nischal KC, et al. Darier's disease following radiotherapy for carcinoma of cervix. *Indian J Dermatol Venereol Leprol.* 2004;70:300-3. [PMID: 17642644].
4. Mac Manus MP, Cavalleri G, Ball DL, et al. Exacerbation, then clearance, of mutation-proven Darier's disease of the skin after radiotherapy for bronchial carcinoma: a case of radiation-induced epidermal differentiation? *Radiat Res.* 2001;156:724–30. [PMID: 11741496].
5. Oakley C, Epstein J., Sherlock C. Reactivation of oral herpes simplex virus. *Oral Surgery, Oral Med Oral Pathol Oral Radiol Endod.* 1997;84:272–8. [PMID: 9377190].
6. Ramirez-Fort MK, Zeng J, Feily A, et al. Radiotherapy-induced reactivation of neurotrophic human herpes viruses: Overview and management. *J Clin Virol.* 2018;98:18–27. [PMID: 29197712].
7. Mackool BT, Goverman J, Nazarian RM. Case 14-2012. *N Engl J Med.* 2012;366:1825–34. [PMID: 22571205].
8. Tayabali K, Pothiwalla H, Lowitt M. Eczema herpeticum in Darier's disease: a topical storm. *J Community Hosp Intern Med Perspect.* 2019;9:347–50. [PMID: 31528287].